学位の種類	博士（医学）
報告番号	甲第１４１０号
学位記番号	第１０１５号
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授与年月日	平成 26 年 3 月 25 日
学位論文の題名	Interleukin-18 may lead to benign prostatic hyperplasia via thrombospondin-1 production in prostatic smooth muscle cells （インターロイキン 18 は前立腺平滑筋細胞におけるトロンボスポンディン 1 の産生を介して前立腺肥大症を誘導しうる） The Prostate. (Accepted for publication)
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Abstract

Background Although inflammation plays an important role in the development of benign prostatic hyperplasia (BPH), little is known about the exact mechanism underlying this pathogenesis. Here, we investigated the relationship between the inflammatory reaction and BPH. **Methods** cDNA microarray analysis was used to identify changes in inflammation-related gene expression in a recently established rat model that mimics human BPH. To investigate the genes identified in the analysis, quantitative (q)RT-PCR, western blotting, immunostaining, and a cell proliferation assay were conducted using BPH model tissues, human prostate tissues, and normal human prostate cultured cells. **Results** Of the 31,100 genes identified in the cDNA analysis, 7 inflammatory-response-related genes were expressed at a >2-fold higher level in rat BPH tissues than in normal rat prostate tissues. The levels of the most commonly expressed pro-inflammatory cytokine, IL-18, significantly increased in rat BPH tissues. In humans, IL-18 was localized in the epithelial and stromal components, while its receptor was strongly localized in smooth muscle cells. Furthermore, in human prostate smooth muscle cell line (PrSMC) , IL-18 effected dose-dependent increases in the phosphorylated Akt and thrombospondin-1 (TSP-1) levels. TSP-1 promoted proliferation of the human prostate stromal cells (PrSC) . **Conclusions** IL-18 may act directly in BPH pathogenesis by inducing TSP-1 production in prostatic smooth muscle cells via Akt phosphorylation. TSP-1 then promotes the proliferation of prostatic stromal cells, which in turn leads to the development of prostatic stromal hyperplasia.